EXHIBIT 4

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EXAMINER	
Bennett Celsa	
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COPY

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action in Ex Parte Reexamination	Control No. 90/007,542	Patent Under Reexamination 6331415	
	Examiner Bennett Celsa	Art Unit 3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

a☒ Responsive to the communication(s) filed on *25 January 2005* . b☐ This action is made FINAL.
c☐ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire 2 month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☒ Information Disclosure Statement, PTO-1449.
3. ☐ Interview Summary, PTO-474.
4. ☐ _____.

Part II SUMMARY OF ACTION

1a. ☒ Claims *1-36* are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled in the present reexamination proceeding.
3. ☐ Claims _____ are patentable and/or confirmed.
4. ☒ Claims *1-36* are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a)☐ approved (7b)☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a)☐ All b)☐ Some* c)☐ None of the certified copies have
   1☐ been received.
   2☐ not been received.
   3☐ been filed in Application No. _____ .
   4☐ been filed in reexamination Control No. _____.
   5☐ been received by the International Bureau in PCT application No. _____.
   * See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: _____

cc: Requester (if third party requester)

Reexamination: NON-Final Office Action

Reexamination of US Patent No. 6,331,415 (Cabilly 2 patent).

Merger of 3rd Partly Requests 90/007,542 and 90/007,859

Procedural Posture:

	i. 90/007542('7542 Proceeding):	ii. 90/007859 ('7859 Proceeding)
Reexamination request filed:	5/13/05	12/23/05
Reexamination ordered:	7/7/05.	1/23/06
Patent Owner Statement:	none	none
First Office Action mailed:	9/13/05	N/A
Patent Owner Response dated	1/25/05.	N/A
'7542 AND '7859 merged:	6/6/06	

Status of the Claims

Claims 1-36 are pending and under reexamination. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

OFFICE ACTION

The First Office Action (mailed 9/13/05) in the 90/007,542 proceeding is hereby withdrawn *in lieu* of the instant office action. The Patentee arguments and declarations presented in response to the First Office Action will be considered in this office action to the extent it is pertinent to the new ground(s) of rejection stated herein.

Information Disclosure Statement (IDS)

The Nov. 28, 2005 IDS has been Examiner initialed. It is noted that:

Once the minimum requirements of 37 CFR 1.97 and 37 CFR 1.98 are met, the examiner has an obligation to consider the information. **It is to be noted, however, that consideration by the examiner of information submitted in an IDS is conducted in the same manner as other documents in Office search files are considered by the examiner while conducting a search of the prior art in a proper field of search.** See MPEP 609, at page 600-125, Revision 2, May 2004. The initials of

the examiner placed adjacent to the citations on the PTO-1449 or PTO/SB/08A and 08B or its equivalent mean that the information has been considered by the examiner to the extent noted above. If there is a reference of particular relevance, the patentee is required to point out the document and its relevance to the Examiner.

Priority

The 6,331,425 Cabilly 2 patent issued on December 18, 2001 from application 07/20541 (filed 6/10/88) which was a continuation of 06/483,457 (filed 4/8/83) now 4,816,567 (Cabilly 1 patent).

The 6,331,415 (Cabilly 2) Invention

The instant patent claims methods and compositions are representative.

i. METHODS:

1. A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell comprising:
(i) transforming said single host cell with a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of the immunoglobulin light chain, and
(ii) independently expressing said first DNA sequence and said second DNA sequence so that said immunoglobulin heavy and light chains are produced as separate molecules in said transformed single host cell. See Claim 1.

33. A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell comprising:
independently expressing a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a. second DNA sequence encoding at least the variable domain of the immunoglobulin light chain so that said immunoglobulin heavy and light chains are produced as separate molecules in said single host cell transformed with said first and second DNA sequences.

21. A method comprising:
a) preparing a DNA sequence consisting essentially of DNA encoding an immunoglobulin consisting of an immunoglobulin heavy chain and light chain or Fab region, said immunoglobulin having specificity for a particular known antigen;
b) inserting the DNA sequence of step a) into a replicable expression vector operably linked to a suitable promoter;

c) transforming a prokaryotic or eukaryotic microbial host cell culture with the vector of step b);
d) culturing the host cell; and
e) recovering the immunoglobulin from the host cell culture, said immunoglobulin being capable of binding to a known antigen.
ii. COMPOSITIONS:

15. A vector comprising a DNA encoding at least a (first) variable immunoglobulin heavy chain domain and a second DNA sequence encoding at least a variable immunoglobulin light chain domain wherein the 1st and 2nd DNA sequences are located at different insertion sites in the vector.

18. A transformed host cell comprising at least two vectors in which one vector comprises a variable immunoglobulin heavy chain domain and a second vector comprises a variable immunoglobulin light chain domain.

32. The insoluble particles of heavy and light chains or Fab region produced by the method of claim 21 in which the heavy and light chains or Fab regions are deposited within the cells (e.g. claim 27).

Art Used In SNQ's Regarding Obviousness Double Patenting

'7542 3rd Party cited references:

1. US Pat. No. 4,816,567 (Cabilly 1): claims 1-7;

2. US Pat. No. 4,399,216 (Axel et al): (issued 3-16-83);

3. EP O 044722 (Kaplan et al.) (published 01-27-82)

4. Accolla et al., PNAS USA 77:563 (1980);

5. Rice and Baltimore, PNAS USA 79 :7862 (1982).

'7542 examiner-cited reference:

6. US Pat. No. 4, 511, 502 (Builder et al.) (issued April 1985).

'7859 3rd Party additionally cited references:

7. Deacon, Biochemical Society Transactions, 4:818-20 (1976).

8. 1982 Valle, Nature, Vol. 300, pp. 71-74 (4 Nov.1982).

9. 1981 Valle, Nature, Vol. 291, pp. 338-340 (28 May 1981).

10. Dallas WO 82/03088.

11. Ochi, Nature, Vol. 302, pp. 340-342 (24 March 1983).

12. Oi PNAS USA, Vol. 80, pages 825-829 (Feb.1983).

Cumulative Prior Art :

The 1982 Valle and Deacon references are cumulative in their teaching of microinjection of mRNA encoding light and heavy immunoglobulin chains into Xenopus oocyte cells to produce secreted active antibody. Accordingly, only the Deacon reference will be utilized in the obviousness double patenting rejection(s) recited below.

Additionally, the Oi and Ochi references are cumulative in their teaching of restoring hybridoma cell antibody expression by vector transformation with a light chain gene. Accordingly, only the Ochi reference will be utilized in the obviousness double patenting rejection(s) recited below.

35 U.S.C. 121 Does Not Preclude Obviousness Double Patenting

The third sentence of 35 U.S.C. 121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent. The 35 U.S.C.121 prohibition applies only where the Office has made a requirement for restriction. The prohibition does not apply where the divisional application was

voluntarily filed by the applicant and not in response to an Office requirement for restriction. See MPEP 804.01. Accordingly, 35 U.S.C. 121 requires claims of a divisional application to have been formally entered, restricted, and removed from an earlier application in order for a patentee to obtain the benefit of 35 U.S.C. 121. *Geneva Pharmaceuticals. Inc. v. GlaxoSmithKline* PLC, 349 F.3d 1373, 1379, 68 USPQ2d 1865, 1870 (Fed. Cir. 2003).

Both 3rd party requesters argue the absence of a 35 U.S.C. 121 bar to double patenting under the instant facts regarding the parent 06/483,457 and sibling 07/205,419 applications which issued as the 4,816,567 (Cabilly I) and 6,331,415 (Cabilly II) patents, respectively. See: '7542 request at pages 10-21; '7859 request at pages 9-11. The requesters argue that 35 USC 121 isn't presently applicable since the Examiner did not make a restriction in the parent 06/483,457 application; and a subsequent Examiner restriction in the 07/205,419 continuation application cannot raise a 121 bar to obviousness double patenting rejection.

The 3rd parties position regarding the absence of a 121 bar to a double patenting rejection in the instant case is consistent with 35 USC 121 and related case law; and the patentee has failed to provide a rebuttal argument to the contrary.

The US Pat. No. 4,816,567 Cabilly 1 Patent Claims:

Construing the Cabilly 1 Patent Claims

a. The '567 Claims

Independent claims 1, 3, 5, and 7 of the '567 patent read as follows;

1. A method comprising

a) preparing a DNA sequence encoding a chimeric immununoglobulin heavy or light chain having specificity for a particular known antigen wherein a constant region is homologous to the corresponding constant region of an antibody of a first mnmmalian species and a variable region thereof is homologous to the variable region of an antibody derived from a second, different mammalian species;
b) inserting the sequence into a replicable expression vector operably linked to a suitable promoter compatible with a host cell;
c) transforming the host cell with the vector of (b);
d) culturing the host cell; and
e) recovering the chimeric heavy or light chain from the host cell culture.

3. A composition comprising a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen having a constant region homologous to a corresponding constant region of an antibody of a first mammalian species and a variable region homologous to a variable region of an antibody derived from a second, different mammalian species.

5. A replicable expression vector comprising DNA operably linked to a promoter compatible with a suitable host cell, said DNA encoding a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen and having a constant region homologous to a corresponding region of an antibody of a first mammalian species and a variable region homologous to a variable region of an antibody derived from a second, different mammalian species.

7. Recombinant host cells transformed with the vector of claim 5.

Claims 2, 4 and 6 (dependent on claims 1, 3 and 5, respectively) recite that the first mammalian species (i.e. the source of the constant region) is human.

b. '567 Claim Interpretation

During reexamination, claims are given the broadest reasonable interpretation consistent with the specification and limitations in the specification are not read into the claims. *In re Yamamoto*, 740 F.2d 1569, 222 USPQ 934 (Fed. Cir. 1984)).

The words of a claim are given their ordinary meaning to one skilled in the art *unless* it appears from the patent and prosecution history that the words were used differently by the inventors. *Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1298, 67 U.S.P.Q.2d 1132, 1136 (Fed. Cir. 2003),.*Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582, 39 U.S.PQ.2d 1573, 1577 (Fed Cir. 1996); *Toro Co. v. White Consol. Indus, Inc.*, 199 F.3d 1295, 1299, 53 U.S.P.Q.2d 1065, 1067 (Fed. Cir. 1999). The ordinary and customary meaning attributed to claim terms may be determined by reviewing various sources, including "the claims themselves; dictionaries and treatises; and the *written description*, the drawings, and the *prosecution history*." *Brookhill-Wilk 1, LLC,* 334 F.3d at 1298, 67 U.S.P.Q.2d at 1136 (citations omitted). Common words, unless the context suggests otherwise, should be accorded their ordinary meaning. *Desper Products, Inc. v. Qsound Labs, Inc.*, 157 F.3d 1325, 1336, 48 U.S.P.Q.2d 1088, 1096 (Fed. Cir. 1998).

Antibodies are proteins which generally refer to tetramers or aggregates thereof having specific immunoreactive activity comprising light and heavy chains in a "Y" configuration (having variable branch and constant stem regions), with or without covalent linkage. '567 patent col. 6, lines 14-18.

Similarly, an "immunoglobulin" generally comprises two heavy and two light chains "but may have specific immunoreactive activity (i.e. an "antibody") or lack such specific immunoreactive activity (i.e. "non-specific immunoglobulin" or "NSI"). See Cabilly I patent col. 6, lines 18-20; and Cabilly 2 patent Fig. 1.

The phrase "chimeric immunoglobulin heavy or light chain" refers to a species of immunoglobulin heavy or light chain in which the constant region is homologous to the constant region of an antibody of a first mammalian species and the variable region is homologous to the variable region of an antibody derived from a second, different mammalian species. See claim 1 and 3 definition;'567 patent col. 6, lines 48-59.

The phrase "replicable expression vector (comprising DNA) operably linked to a suitable promoter compatible with a host cell" of Cabilly 1 claims 1 and 5 is discussed in the '567 patent specification. An "expression vector" includes:

> ... vectors which are capable of expressing DNA sequences contained therein, i.e., the coding sequences are operably linked to other sequences capable of effecting their expression. It is implied, although not always explicitly stated, that these expression vectors must be replicable in the host organisms . . . .
>
> '567 patent, col. 8, 11. 21-27.

"Host cells," as recited in Cabilly 1 claims 1 and 7, include prokaryotic or eukaryotic cells, including eukaryotic microbes, and cells derived from multicellular organisms, such as mammalian cells. See '567 patent, col. 8, line 46 to col. 10, 1ines 13-30, 57

The final step of the Cabilly 1 claim 1 process calls for "recovering the chimeric heavy or light chain from the host cell culture": "[t]he protein thus produced is then

recovered from the cell culture by methods known in the art, but the choice of which is necessarily dependent on the form in which the protein is expressed. " '567 patent, col. 13, lines 3-6.

The recombinant procedures used to obtain the DNA sequences, prepare vectors, transform cells, culture cells, and recover the immunoglobulins are the same, whether for recombinant immunoglobulins that mimic naturally occurring ones or for altered recombinant immunoglobulins, such as chimeric antibodies. See e.g., '567 patent, col. 15, lines 59 to col. 16, line 15; and col. 28, lines 44-47.

c. The Cabilly 1 Claims Read on Expressing Both Heavy and Light Chains Together, and Each Separately.

The 4,816,567 Cabilly 1 patent claims use the conjunction "or" when referring to the "heavy or light chain".

Although, normally the conjunctive term "or" is interpreted to mean that the items in a sequence are alternatives to each other (e.g. *Brown v. 3M*, 265 F.3d 1349,1352, 60 U.S.P.Q. 2d 1375,1377 (Fed. Cir. 2001) **the patentee can be his/her own lexicographer and impart a different meaning**. *Kustom Signal Inc. v. Applied Concepts Inc.*, 264 F.3d 1326,1331, 60 U.S.P.Q. 2d 1135,1138 (Fed. Cir. 2001) (emphasis provided). See also Vitronics Corp. v. Conceptronic, Inc., 90 F. 3d 1576,1582, 39 U.S.P.Q.2d 1573,1576 (Fed. Cir. 1996)("[A] patentee may choose to be his own lexicographer and use terms in a manner other than their ordinary meaning, as long as the special definition of the term is *clearly stated in the patent specification or file history*.").

Both the reference Cabilly I (4,816,567) patent specification and the its file history support construing "or" to be "and/or.

During the prosecution of the reference Cabilly 1 patent application, applicant in an amendment dated October 28, 1985, cancelled original claims 1-52 and added the following new claims 53, 57, 65 and 68 (among others):

53. A method **comprising**

a) preparing a DNA sequence encoding an immunoglobulin heavy **or** light chain, or an immunoglobulin Fab region, of known specificity;
b) inserting the sequence into a replicable expression vector operably linked to a suitable promoter;
c) transforming a prokaryotic or eukaryotic microbial host cell culture with the vector of b); and
d) recovering mature heavy chain, light chain or Fab from the host cell culture unfused to a portion of the amino acid sequence of a host cell-homologous polypeptide.

57. The method of claim 53 wherein the vector contains DNA encoding **both a heavy chain and a light chain**.

65. The method of claim 53 wherein **the heavy and light chain are co-expressed in the same host**.

68. A method **comprising**

a) preparing a DNA sequence encoding a chimeric immunoglobulin heavy **or** light chain of known specificity wherein the constant regions are homologous to the corresponding constant regions of an antibody of a first mammalian species and the variable regions are homologous to the variable regions of an antibody derived from a second, different mammalian species;
b) inserting the sequence into a replicable expression vector operably linked to a suitable promoter;
c) transforming a prokaryotic or eukaryotic microbial host cell culture with the vector of b); and
d) recovering the chimeric heavy chain or light chain from the host cell culture.

(emphasis provided).

Claim 68 above is essentially identical to issued claim 1.

The amendment provide support for new claims 53, 57 and 65 in tabular form as follows:

NEW CLAIM NO.	(specification page/line or original claim)
53	51; 52; 10/30; 12/4;7/25-31
	* * *
57	22/29-33
	* * *
65	23/29

Original claim 51 was drawn to preparing heavy chain or light chain comprising:

a) preparing a DNA sequence encoding heavy or light chain,
b) inserting said sequence into a replicable expression vector operably linked to a suitable promoter,
c) transforming host cell culture with the vector of b) and
d) recovering heavy or light chain from cell culture.

The '567 patent specification support relevant to claims 57 and 65 are:

a. page 22, lines 29-33;

> In the present invention, the gene coding for the light chain and that coding for the heavy chain are recovered separately by the procedures outlined above.Thus they may be inserted into separate expression plasmids, or together ïn the same plasmïd,so long as each is under suitable promoter and translation control.

b. page 23, lines 1-7:

> The expression vectors constructed above are then used to transform suitable cells. The light and heavy chains may be transformed into separate cell cultures, either of the same or of differing species; separate plasmids for light and heavy chain may be used to co-transform a single cell culture or, finally, a single expression plasmid containing both genes and capable of expressing the genes for both light and heavy chain may be transformed into a single cell culture.

c. page 23, lines 29-33

> When heavy and light chain are coexpressed in the same host, the isolation procedure is designed so as to recover reconstituted antibody. This can be accomplished in vitro as described below, or might be possible in vivo in a microorganism which secretes the IgG chains out of the reducing environment of the cytopl asm. A more detailed description is given in D.2, below.

Accordingly, newly presented claim 53 in the Cabilly 1 application defined "or" to be "and/or" when referring to immunoglobulin heavy and light chains and their expression in order to encompass specification embodiments where:

a. light chain and heavy chain encoding DNA is inserted into 2 separate vectors for individual expression in 2 different hosts ("or" embodiment);

b. light chain and heavy chain encoding DNA is inserted into 2 separate vectors for coexpression of both vectors into 1 host (claim 65 "and" embodiment);

c. light chain and heavy chain encoding DNA are inserted into 1 vector for expression in 1 host (claim 57 "and" embodiment).

Additionally, the '567 patent claims utilize the transitional term "comprising" which opens the claim to the inclusion of additional, unrecited elements or method steps necessary to effect the described (and claimed) "**and**/or" embodiments. *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364,1368, 66 U.S.P.Q.2d 1631, 1634 (Fed. Cir. 2003) (defining "comprising").

Thus, by analogy to claim 53 introduced during the 06/483,457 application prosecution, the claim 68 (which corresponds to reference Cabilly patent claim1) phrase "heavy **or** light chain" means heavy **and/or** light since it includes embodiments where both chains are present in the same host cell, even on the same DNA

construct i.e. the Cabilly I claims encompass independent expression in one host of light and heavy immunoglobulin chains utilizing two separate vectors or the use of a single vector encoding both immunoglobulin heavy and light chains, as well as the resulting vector constructs.

OBVIOUSNESS DOUBLE PATENTING .

New Rejection(s)

1. Claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 of U.S. Pat. No. 6,331,415 (Cabilly 2) are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 4,816,567 (3/89: Cabilly1) (*wherein "or" is being interpreted as "and/or" in light of the Cabilly 1 patent prosecution history).*

Both the Cabilly 1 and the instant Cabilly 2 patented inventions include claims directed to the same statutory subject matter: recombinant processes, vectors and host cells for making immunoglobulins (particularly chimeric immunoglobulins), and immunoglobulin products.

The Reference Cabilly 1 Patent:

The reference Cabilly 1 patented invention is drawn to (claim 1) a method comprising

a) preparing a DNA sequence encoding a chimeric immununoglobulin heavy or light chain having specificity for a particular known antigen wherein a constant region is homologous to the corresponding constant region of an antibody of a first mammalian species and a variable region thereof is homologous to the variable region of an antibody derived from a second, different mammalian species;

b) inserting the sequence into a replicable expression vector operably linked to a suitable promoter compatible with a host cell;
c) transforming the host cell with the vector of (b);
d) culturing the host cell; and
e) recovering the chimeric heavy or light chain from the host cell culture.

In the reference Cabilly 1 disclosure, "immunoglobulins" are defined as being comprised of light (kappa or lambda) and heavy chains (gamma, mu, alpha, delta or epsilon), which if when assembled possess "specific immunoreactive activity" are labeled "antibodies". See Cabilly 1 at col. 3, lines 15-42; col. 6, lines 14-24. The phrase "chimeric immunoglobulin heavy or light chain" refers to a species of immunoglobulin heavy or light chain in which the constant region is homologous to the constant region of an antibody of a first mammalian species and the variable region is homologous to the variable region of an antibody derived from a second, different mammalian species. See Cabilly 1 patent: claims 1 and 3; and col. 6, lines 48-59. The Cabilly I patent includes mammalian chimeric immunoglobulin light and heavy chains which are derived from humans (dependent claims 2 and 4). Mammalian antibody sources are derived *in situ* from mammalian B lymphocytes or from cell culture hybridomas. See Cabilly 1 patent col. 1, lines 38-42. The claimed "(replicable) expression vector" is defined as vectors capable of expressing DNA sequences contained therein which are frequently in the form of plasmids, thus 'plasmid' and 'expression vector' are often used interchangeably. See Cabilly 1 patent col. 8, lines 21-45. "Host cells" include prokaryotic (most preferably the gram (-) bacteria E. Coli. Strains ATCC: 31446 and 31537) or eukaryotic cells, including eukaryotic microbes, and cells derived from

multicellular organisms, such as mammalian cells. See Cabilly 1 patent , col. 8, 1ine 46 to col. 10, lines 13-30, 57. The means of recovery of successfully transformed chimeric heavy or light chains is determined by the type of protein and host organism but utilizes art known techniques including cell lysis of insolubilized particles present in the host followed by denaturant solubilization. See Cabilly 1 patent col. 4, lines 27-35.

The Cabilly 1 reference patented invention *differs from* the instant patent since:

a. reference Cabilly 1 produces a (replicable expression) vector comprising DNA encoding immunoglobulin heavy **or** light chain for transforming and culturing of a host cell; whereas the instant patent requires that the vector comprise DNA encoding immunoglobulin heavy **and** light chain for transforming and culturing of a single host cell [1] and

b. reference Cabilly 1 is directed to the production of chimeric immunoglobulins (i.e. a species); whereas the instant invention produces an immunoglobulin (i.e. is generic);

Regarding item a, as discussed *supra*, the Cabilly I reference patent claims (using "or") read on expressing both heavy and light chains together ("and") as well as expressing heavy or light chains separately in different vectors ("or") since both the Cabilly 1 patent specification and prosecution history provide support for this interpretation. See amendment dated October 28, 1985 in 06/483,457 application (issued as the '567 Cabilly 1 patent) canceling original claims 1-52 and adding new

[1] The Cabilly 2 transforming limitation of "at least the variable domains of the immunoglobulin heavy and light chains" as applicable to making an immunoglobulin (as compared to a fragment) would encompass the entire light and heavy chain as in the Cabilly 1 patent.

claims 53, 57, 65 and 68. Additionally, the reference Cabilly 1 patent claims utilize the transitional term "comprising" which opens the claim to the inclusion of additional, unrecited elements or method steps necessary to effect the described (and claimed) "**and**/or" embodiments. *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364,1368, 66 U.S.P.Q.2d 1631, 1634 (Fed. Cir. 2003) (defining "comprising"). Accordingly, the Cabilly I patent claims when referring to immunoglobulin heavy and light chains and their expression encompass specification embodiments where:

a. light chain and heavy chain encoding DNA is inserted into 2 separate vectors for individual expression in 2 different hosts ("or" embodiment);
b. light chain and heavy chain encoding DNA is inserted into 2 separate vectors for coexpression of both vectors into 1 host ("and" embodiment);
c. light chain and heavy chain encoding DNA are inserted into 1 vector for expression in 1 host ("and" embodiment).

Additionally, the steps to produce an assembled recombinant chimeric immunoglobulin in the Cabilly 1 reference patent process, necessarily involve analogous processes, vectors, and host cells as in the instant invention. The reference Cabilly 1 specification explains that immunoglobulins result from assembly, whether in the cell or *in vitro*, of heavy and light chains. The means of recovery of successfully transformed chimeric heavy or light chains is determined by the type of protein and host organism but utilizes art known techniques including cell lysis of insolubilized particles present in the host (e.g. gram-negative E.Coli.) followed by denaturant solubilization; unless the host organism normally secretes the protein out of the cell (e.g. some yeast and gram positive bacteria). See reference Cabilly 1 patent col. 4, lines 27-35; col. 12,

line 66-col. 13, line 18. The reference Cabilly 1 patent specification discloses expressing heavy and light chains preferably for immunoglobulin assembly, a utility which is supported by the reference Cabilly 1 claimed antigen specificity of its chains; and thus it is appropriate to construe the reference Cabilly 1 patent claims to encompass production of chimeric immunoglobuins (i.e. antibodies) using recombinant technology, and vectors and host cells for doing so. *Geneva Pharmaceuticals, Inc.*, 349 F.3d at 1385, 68 U.S.P.Q. 2d at 1875. Thus, modification of the reference Cabilly 1 patented invention to effect the expression of immunoglobulin heavy and light chains in a single host to form a functional antibody would have been obvious to one of ordinary skill in the art at the time the instant invention was made.

Turning to item b. above, the instant Cabilly 2 patented generic invention drawn to producing an immunoglobulin clearly encompasses the chimeric immunoglobulin species as evidenced by instant patent claims 2 and 13 drawn to the definition of a chimeric immunoglobulin. Obviousness-type non-statutory double patenting can arise when a later claim covers a genus and an earlier claim covers a species within the genus. *In re Berg*, 140 F.3d at 1437, 46 U.S.P.Q. at 1233 (Fed. Cir. 1998).

Detailed Analysis: Obviousness of Claims 1-4, 11, 13, 15-18, 21, 23-25 and 33:

a. Instant Claims 1, 13, 15-18, 21 and 33 are obvious

Instant claims 1, 21 and 33 are drawn to methods for producing a genus of immunoglobulins; while Cabilly claim 1 is directed to methods for producing "chimeric" immunoglobulin chains, which is a species of the instant immunoglobulin genus. The same applies to the vector (claim 5) and host cell (claim 7) claims of the Cabilly 1 patent

reference and corresponding claims 15-16 (vector) and 17-18 (host cell) of the instant Cabilly 2 patent. Further, claim 1 of the reference Cabilly 1 patent recites a chimeric immunoglobulin species of the sub-genus defined by claim 13 of the Cabilly 2 patent and claims 2 and 6 of the reference Cabilly 1 patent are directed to a human constant region of the chimeric immunoglobùlin which is another example of a species within the genus claimed in the instant patent. Patentee is reminded that the term "comprising" recited in claim 1 of the earlier Cabilly 1 patent is inclusive or open-ended and does not exclude additional, unrecited elements or method steps (MPEP 2111.03). Thus, while the claims of the reference Cabilly 1 patent embrace embodiments in which separate host cell cultures express either a chimeric heavy or a chimeric light immunoglobulin chain, the claims also read on embodiments in which one host cell culture expresses both the heavy and light chains, at least one of which is chimeric. Thus, claims 1-2 and 5-7 of the reference Cabilly 1 patent read upon claims 1, 13, 15-18, 21 and 33 of the instant Cabilly 2 patent.

b. Instant claims 2-3, 11 and 25 are obvious

Instant claim 2 provides for heavy and light chains to be present in different vectors while claim 3 requires both to be present in a single vector.

Instant claims 11 and 25 requires that the (vector) DNA sequences code the heavy and light chains.

As discussed *supra*, the Cabilly 1 claim interpretation of "or" as being "and/or" when referring to chimeric immunoglobulin heavy and light chains and their expression encompass, and thus render obvious, specification embodiments where:

a. light chain and heavy chain encoding DNA is inserted into 2 separate vectors for individual expression in 2 different hosts ("or" embodiment);

b. light chain and heavy chain encoding DNA is inserted into 2 separate vectors for coexpression of both vectors into 1 host ("and" embodiment);

c. light chain and heavy chain encoding DNA are inserted into 1 vector for expression in 1 host ("and" embodiment).

c. Instant claim 4 is obvious

Instant claim 4 utilizes a plasmid as a vector.

As discussed *supra*, in the Cabilly 1 patent claims, the phrase"(replicable) expression vector" is defined as vectors capable of expressing DNA sequences contained therein which are frequently in the form of plasmids, thus 'plasmid' and 'expression vector' are often used interchangeably . See '567 patent col. 8, lines 21-45. Accordingly, the Cabilly 1 patent claims use of the term "vector" renders obvious the selection of a plasmid as a vector since both terms are used interchangeably.

d. Instant claims 23 and 24 are obvious

Instant claim 23 is drawn to gamma heavy chain.

Instant claim 24 is drawn to kappa light chain.

As discussed *supra*, the Cabilly 1 patent claimed "heavy or light chain immunoglobulins" which are defined as being comprised of light (kappa or lambda) and heavy chains (gamma, mu, alpha, delta or epsilon), which when assembled, possess "specific immunoreactive activity" and are termed "antibodies". See '567 at col. 3, lines 15-42; col. 6, lines 14-24). Thus, the small number of different light and heavy chains

within the scope of the Cabilly 1 patent claims render obvious the selection of gamma heavy chains and kappa light chains as instantly claimed.

2. Claims 1-36 of U.S. Pat. No. 6,331,415 (Cabilly 2) are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 4,816,567 (Cabilly 1) as applied to claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 (*wherein "or" is being interpreted as "and/or" in light of the Cabilly 1 patent prosecution history)* and further in view of *Axel et al.* U.S. Pat. No. 4,399,216 (8/83), *Rice et al.* PNAS USA 79 (12/82):7862-7865, *Kaplan et al.* EP 004722 (1/82), *Builder et al.* U.S. Pat. No. 4,511,502 (issued 4/85), *Accolla et al.* PNAS USA 77(1): 563-566 Dallas (WO 82/03088), Deacon (Biochemical. Society Transactions, 4 (1976):818-820), *1981 Valle* (Nature, 291 (May '81) pages 338-340; and *Ochi* (Nature, 302 (3/24/83) pages 340-342).

The double patenting rejection of claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 of the instant Cabilly 2 patent over claims 1-7 of reference Cabilly 1 patent is discussed *supra.*

As discussed *supra*, Cabilly 1 claims recombinant processes, vectors and host cells for making chimeric immunoglobulins (and immunoglobulin products), which is a species within the instant claimed genus of immunoglobulins. Since the heavy chain or light chain is recovered from the host cell culture, the heavy or light chain was expressed in the cell. As a result, the reference Cabilly 1 claims teach the independent expression of a chimeric heavy chain or chimeric light chain in a host cell, and a vector that contains such chimeric heavy or light chains.

Claim Interpretation 1: Reference Cabilly 1 Patent's "or" encompasses "and"; thus rendering obvious claims 1-4, 11, 13, 15-18, 21, 23-25 and 33:

As discussed *supra*, the recitation of the Cabilly I reference patent claims (using "or") reads on *expressing both* heavy and light chains together ("and") as well as expressing heavy or light chains separately in different vectors ("or") since both the Cabilly 1 patent specification and prosecution history provide support for this interpretation. Accordingly, for the reasons discussed *supra*, claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 are obvious over the reference Cabilly 1 patent claims.

Claim Interpretation 2: Even if the reference Cabilly 1 patent claim's use of "or" does not include "and"; claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 are nevertheless rendered obvious in light of prior art:

Alternatively, regarding claims 1-4, 11, 13, 15-18, 21, 23-25 and 33, even if the Cabilly 1 patent teaching of producing immunoglobulin heavy **or** light chain is restricted to the separate recombinant production of light or heavy chains in separate host cells, the instant Cabilly 2 patent expression of a heavy and light chain (using one or two vectors) in a single host cell would nevertheless have been obvious for the following reasons.

i. One of ordinary skill in the art would have been motivated to express, in a single host, light and heavy immunoglobulin chains (using one or two vectors) when viewing the reference Cabilly 1 patented invention in light of the prior art

Axel et al. teach a process for inserting foreign DNA into eukaryotic cells by co-transforming the cells with this foreign DNA and an unlinked DNA that codes for a

selectable phenotype not otherwise expressed by the cell (see col. 3, lines 21-27). Axel describes the process as particularly suited for the transformation of DNA into eukaryotic cells for making antibodies (see col. 3, lines 31-36). Axel discloses and claims the expression of antibodies in mammalian host cells as intact (assembled) proteins. See *Axel:* abstract; col. 5, lines 3-7 and 24-28; patent claims 1, 7, 22-24, 28 and 29.

Rice introduced a recombinant rearranged murine kappa light chain gene construct into an Abelson murine leukemia virus (A-MuLv)-transformed lymphoid cell line which already synthesized y2b heavy chain protein (see page 7862). *Rice* inserted the light chain gene into a plasmid, transfected the cells, and then examined the polypeptides as well as the RNA produced by the cells (see pages 7863-7864 and Figures 2 and 3). Lastly, since the cells were producing both immunoglobulin light and heavy chains, the cells were examined for the ability to assemble the chains into IgG molecules, leading to the observation that "[e]ssentially all of the k chain produced in the K-2 cells appear to be assembled into IgG2b" (see page 7864 and Abstract penultimate sentence). Thus, *Rice* demonstrates the successful expression of both heavy and light chains in a host with subsequent assembly into immunoglobulins.

Kaplan teaches that human hybridomas can serve as a useful source of mRNA encoding the antibody heavy and light chains to specific antigens. By using known molecular biology techniques, the mRNA's can be used for the generation of genes which, when inserted into the appropriate vector, can serve as a coding source for the production of proteins (see page 3, lines 4-9). In addition, *Kaplan* teaches that a variety

of host cells (e.g. bacteria and yeast) and plasmids (particularly pBR322) may be used to express recombinant heavy and light chains (see page 10, lines 1-33).

Dallas teaches that two different proteins (in addition to a selectable marker) can be expressed in a single cell and such expression may be accomplished by the use of two vectors, each containing DNA encoding one of the proteins, or by use of a single vector that contains DNA encoding each of the proteins. (See Example IV, as well as page 8, lines 9-11, which disclose the use of a single vector, and page 9, lines 27-29, which discloses the use of two vectors). More particularly, a plasmid containing a HindIII DNA fragment encoding one protein was subcloned into a separate site of a second plasmid containing a BamHI DNA fragment encoding a second protein to form a single plasmid used for independently expressing both proteins in a single cell. See page 8, lines 11-17 and page 7, lines 29-33.

Thus, the *Axel, Rice* and *Kaplan* references taken in view of the *Dallas* reference teaching would provide motivation to one of ordinary skill in the art at the time the instant invention was made to modify the Cabilly 1 patented invention to transform a single host with

a. the individual Cabilly 1 vectors separately containing a light or heavy chain; or

b. a modified Cabilly 1 vector encoding both an immunoglobulin light and heavy chain for independent expression of these chains.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify the Cabilly 1 patented invention so as to cotransform a single host with two vectors each containing DNA encoding a light or

heavy chain, or to utilize a single vector containing both light and heavy chain DNA in order to transform a host cell to independently express said DNA sequences as in Cabilly 2 patent claims 1, 15, 18, 21 and 33 (and claims dependent thereon).

ii. The prior art provides further motivation to make active antibody with a reasonable expectation of success.

The *Deacon* and *1981 Valle* references introduced and expressed exogenous light and heavy chains into eukaryotic cells achieving assembled functional immunoglobulins. Additionally, the *Ochi* reference restored specific antibody production by cloning light immunoglobulin chain into a cell line endogenously producing heavy immunoglobulin chain.

More specifically, *Deacon* teaches injecting mRNA encoding heavy and light immunoglobulins (to hemocyanin or ferritin antigen) into *Xenopus* (frog) oocytes (see Abstract; and page 818 for procedure) and concludes (page 829, lines 1-5) that "mRNA from hyperimmunized rats, when injected into oocytes, is translated into heavy and light chains" and that "in oocytes, heavy and light chains can be assembled into immunoglobulin molecules, which can behave as antibodies directed against antigen".

Similarly, *1981 Valle* taught that microinjection of mRNA encoding light (kappa) and heavy (gamma 1) chains from immunoglobulin MOPC21 (produced by mouse plasmacytoma P3/X63 cell line) into Xenopus oocytes resulted in oocyte assembly and secretion of tetrameric mouse immunoglobulin upon addition of horse serum to the oocyte medium to prevent "gratuitous oxidation". See *Valle* Abstract, page 338, col. 2; page 339, col. 2; and Figure 2B, Track 4 showing secreted tetrameric antibody.

Although the above-discussed *Deacon* and *1981 Valle* reference utilize m-RNA, as compared to the use of vector DNA in the Cabilly 1 claims for encoding the corresponding light and heavy immunoglobulin chains, once the m-RNA or vector DNA is expressed, the ability of the two chains to assemble into an immunoglobulin does not depend on the genetic material used for such expression. Accordingly, the difference between using vector DNA vs. mRNA for host transformation is not substantive.

Additionally, *Ochi* discloses that an exogenous light immunoglobulin chain specific for 2,4,6-trinitrophenyl (TNP) cloned into a mammalian cell (mutant igk-14 producing heavy chain specific for TNP but not light chain) results in the cell's assembly and secretion of a functional immunoglobulin (i.e. binds TNP). See Abstract; Figures 1 and 2; last full paragraph on page 340; and Table 1).

Accordingly, the *Deacon, 1981 Valle* and *Ochi* references taken separately or in combination provide further motivation to perform the Cabilly 1 patented steps in a single cell for producing a chimeric heavy and light chain which is assembled into active antibody thus rendering obvious the production of a functional immunoglobulin with a reasonable expectation of success to one of ordinary skill in the art at the time the instant invention was made.

***Obviousness of Dependent Claims* 5-10, 12, 14, 19-20, 22, 26-32 and 34-36**

The Cabilly 1 patent claims (under claim interpretation 1 or 2 above) render obvious dependent claim 5-10, 12, 14, 19-20, 22, 26-32 and 34-36 for the following reasons.

The Cabilly 1 patented invention teaching **differs** from the instant claims by:

a. using vector plasmid pBR322 (claim 5);

b. using bacterial/yeast/mammalian host cells including E Coli strain X1776 (claims 6-8, 19, 20, and 26);

c. secretion from transformed host (e.g. mammalian) of a functional immunoglobulin (claims 9 and 29);

d. insolubilized antibody in the transformed host (e.g. E.Coli) which is solubilized and refolded to form functional immunoglobulin (claims 10 and 27-32)

e. same source for DNA of constant and variable domains (claim 12)

f. mononclonal DNA source of constant and variable domains (claim 14)

g. transforming an anti-CEA antibody (claim 22); and

h. attaching drug or label to the immunoglobulin molecule (claims 34-36).

a Instant claim 5 is obvious

As discussed *supra*, the Cabilly 1 claimed "(replicable) expression vector" is interchangeable with "plasmid" due to the frequent use of these vectors. *Axel* (col. 8, lines 7-35) and *Kaplan* (page 10) teach using plasmids, particularly pBR322, for expressing heterologous proteins thus rendering the use of this particular plasmid species obvious for use in the Cabilly 1 patented recombinant methods.

b. Instant claims 6-8, 19, 20 and 26 are obvious

Claim 6 of the instant patent recites that the host cell is a bacterium or yeast. Claim 7 recites that the host cell is E. coli (a bacterium) or *S. cerevisiae* (a yeast), and claim 8 recites that the bacterial host cell is *E. coli* strain X1776. Claims 19 and 20 recite mammalian host cells. Claim 26 recites that the host cell is E. coli or yeast.

Each of these host cells is a host cell within the scope of claim 1 of the reference Cabilly 1 patent. *Axel* teaches mammalian host cells for expressing proteins, particularly antibodies. *Axel*, col. 5, lines 3-7 and 24-28. *Rice* demonstrates expression of a recombinant immunoglobulin light chain in a mammalian host cell. *Rice,* p. 7863. *Kaplan* teaches bacteria and yeast host cells for expressing recombinant immunoglobulin chains (*Kaplan*, p.10, lines 1-33). Thus, the instant Cabilly 2 patent claims 6-8, 19, and 26 are obvious variants of the reference Cabilly 1 patent claims.

c. Instant claims 9 and 29 are obvious

Instant claims 9 and 29 are drawn to expression and secretion of an immunologically functional immunoglobulin.

The reference Cabilly 1 patent claims encompass expressing immunoglobulin proteins in host cells that are capable of secreting immunologically functional immunoglobulins. Cabilly 1 "host cells" include prokaryotic (most preferably the bacteria *E. Coli.*) or eukaryotic cells, including eukaryotic microbes, and cells derived from multicellular organisms, such as mammalian cells. See Cabilly 1 patent, col. 8, 1ine 46 to col. 10, lines 13-30, 57. In this regard, the Cabilly 1 patent claims encompass recovery of chimeric light or heavy chains by:

a. cell lysis of insolubilized particles present in the host followed by denaturant solubilization; or

b. host cell secretion of active protein.

See Cabilly 1 patent col. 4, lines 27-35; col. 12, line 66-col. 13, line 18

Axel teaches mammalian host cells for expressing heterologous proteins, including antibodies. See *Axel*: abstract; col. 5, lines 3-7 and 24-28; patent claims 1, 7, 22-24, 28 and 29. *Rice* demonstrates expression of a recombinant immunoglobulin light chain in a mammalian host cell (*Rice* page 7863). Thus, the selection of host cells capable of secreting proteins for use in the Cabilly 1 patented invention would have represented an obvious design choice in view of the *Axel* and/or *Rice* references.

d. Instant claims 10 and 27-32 are obvious

Instant claims 10 & 27-32 are drawn to expressing insolubilized antibody in the transformed host (e.g. *E.Coli*) that is solubilized and refolded to form immunoglobulin.

The Cabilly 1 patent claims encompass expressing immunoglobulin proteins in host cells (e.g. E. Coli) in insoluble form which is then solubilized and refolded to form functional immunoglobulin. Cabilly 1 "Host cells" include prokaryotic (most preferably the bacteria E. Coli.) or eukaryotic cells, including eukaryotic microbes, and cells derived from multicellular organisms, such as mammalian cells. See '567 patent, col. 8, 1ine 46 to col. 10, lines 13-30, 57. In this regard, the Cabilly patent claims encompass recovery of chimeric light or heavy chains by:

a. cell lysis of insolubilized particles present in the host followed by denaturant solubilization; or

b. host cell secretion of active protein.

See Cabilly 1 patent col. 4, lines 27-35; col. 12, line 66-col. 13, line 18.

Kaplan teaches bacteria and yeast cells for expressing recombinant immunoglobulin chains (p. 10, lines 1-27) and *Kaplan* also describes rupturing the host

cells, isolating the heavy and light chains and combining them under mildly oxidative conditions to promote refolding and disulfide bond formation. See *Kaplan* at page 10, lines 1-33.

Similarly, *Builder et al.* teach expression of exogenous or foreign proteins in host cells (e.g. bacteria) in insoluble form that is recovered, solubilized and refolded. See *Kaplan* columns 2-6 and Schemes 1 and 2.

Thus, the instant patent claims *10 and 27-32* are obvious variants of the reference Cabilly 1 patent claims in view of *Kaplan* and/or *Builder*.

e. Instant claim 12 is obvious

Claim 12 of the instant patent requires that the constant and variable domains be derived from the same source of DNA.

Although the reference Cabilly 1 patent is directed to utilizing DNA encoding heavy or light chains from different sources (e.g. chimeric), it would have been obvious to utilize heavy or light chain DNA from the same source in light of the use of same source DNA as taught by both the *Kaplan* (e.g. from human hybridomas) and/or the *Rice* reference (e.g. from mice), especially since non-chimeric expression was conventional in the art.

f. Instant claim 14 is obvious

Claim 14 of the instant patent requires that the constant and variable domains be derived from one or more monoclonal antibody producing hybridomas.

Kaplan teaches that human hybridomas can serve as a useful source of mRNA encoding the antibody heavy and light chains (including variable and constant domains)

to specific antigens. By using known biology techniques, the mRNAs can be used for the generation of genes which, when inserted into the appropriate vector, can serve as a coding source for the production of proteins (see *Kaplan* page 3, lines 4-9). In addition, *Kaplan* teaches that a variety of host cells (e.g. bacteria and yeast), may be used to express such recombinant immunoglobulin heavy and light chains (see page 10, lines 1-33). Accordingly, employing monoclonal antibodies as a source of DNA encoding heavy and light chains (variable and constant domains) would have been obvious in light of the *Kaplan* teaching.

g. *Instant claim 22 is obvious*

Claim 22 of the instant patent limits the method of claim 21 to making an anti-CEA (i.e. an antibody to carcinoembryonic antigen).

CEA is an antigen within the general scope of a "particular known antigen" of the reference Cabilly patent claim 1. Additionally, the instant Cabilly 2 patentee admits that anti-CEA antibodies are useful for tumor detection and perhaps use in treating tumors that have CEA at their surface. See Cabilly 2 patent, col. 16, lines 31-38 and references cited therein.

Additionally, *Accola* et al. describes making anti-CEA monoclonal antibodies.

Accordingly, instant claim 22 represents an obvious variant of the reference Cabilly 1 patented invention in light of the reference Cabilly 1 patented claimed teaching and the art-recognized motivation to make claim 22 CEA antibodies for diagnostic or therapeutic purposes.

h. Instant claims 34-36 are obvious

Claims 34-36 (dependent on 9, 10 and 33) further include attaching a label or drug to the immunoglobulin.

Kaplan (page 8, lines 7-21) teaches the use of antibodies for site directed therapy (i.e. via drug attachment) or diagnostic use (i.e. via label attachment for localization).

Accordingly, it would have been obvious to modify the reference Cabilly 1 claimed antibodies to attach a drug and/or label for use in therapy and/or diagnostics, respectively.

Examiner Rebuttal of Arguments Presented in the Patentee Response (1/25/05)

1. Patentee argues that the findings of the PTO during prosecution of the '415, '567 and Boss Patents establish that the instant Cabilly 2 ('415) patent claims are patentably distinct from the claims of the reference Cabilly 1 ('567) patent. The Patentee particularly cites the Board's failure to introduce the Cabilly 1 patent claims into the interference between the Cabilly 2 (copied) claims and the Boss patent claims; and additionally an interview conducted on October 4, 2001 during the Cabilly 2 patent prosecution indicating the failure of the Examiner to raise double patenting between the Cabilly 1 and 2 patent claims.

This argument is not persuasive since a substantial new question of patentability with respect to obviousness double patenting is being based on newly cited references and a combined teaching with the reference Cabilly 1 patent claims neither of which was considered by the Examiner in the earlier concluded examination(s) nor by the Board judges in the interference proceeding. MPEP 2258.01.

2. Patentee presents a132 Declaration by Dr. Riggs in order to establish that the separate recombinant production of immunoglobulin light or heavy chains was useful to raise monospecific antisera for diagnostic use, such as to clinically diagnose and monitor multiple myeloma. Additionally, in the 132 Declaration Dr. Timothy John Roy Harris provides his opinion that the phrase "having specificity for a particular known antigen" in the reference Cabilly 1 patent "does not mean that the individual chimeric immunoglobulin chain must exhibit-by itself-antigen binding functionality, or that the chimeric chain must be incorporated into an immunoglobulin molecule or immunologically functional fragment.

These arguments were not deemed persuasive for the following reasons.

The reference Cabilly I patent (col. 1, lines 30-35; and col. 1, lines 14-23) describes two types of immunoglobulins:

a. non-specific immunoglobulins which lack antigen specificity and are "produced at low levels by the lymph system and in **increased levels by myelomas"** (emphasis); and

b. immunoglobulins containing assemblies of light and heavy chains which have specific immunoreactive activity.

Accordingly in light of the reference Cabilly 1 specification it is reasonable to interpret the Cabilly 1 claimed phrase "immunoglobulin heavy or light chain **having specificity for a particular known antigen**" as *suggesting* the use of the Cabilly 1 claimed "specific" immunoglobulins for assembly into antibodies; in contradistinction to the alternate use of *non-specific* immunoglobulins for the diagnosis of myelolma. However, it is also noted that both the reference Cabilly 1 and instant patent claims encompass both utilities unless the claims specifically recite otherwise.

3. The Harris 132 Declaration argues that the Axel reference does not suggest processes for producing and isolating multiple different polypeptides from a transformed host cell but only a single protein (encoded by DNA I) and a selectable marker (encoded by DNA II). Thus it is argued that Axel does not teach (nor can it be modified to teach) encoding both a light and heavy chain protein in a transformed host cell. It is further argued that the Axel reference although mentioning "antibodies" as exemplified polypeptide, fails to disclose procedures for producing immunoglobulin molecules or immunologically functional fragments having both heavy and light chains

These arguments were not deemed persuasive for the following reasons.

Initially it is noted that in response to patentee's arguments against the reference(s) individually, one cannot show nonobviousness by attacking reference(s) individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Additionally, the Axel reference suggests expressing two immunoglobulin chains in a single cell, since Axel discloses and claims (e.g. claim 7) DNA (i.e. DNA1) encoding an antibody that necessarily possesses both light and heavy immunoglobulin chains. In this respect, the Axel reference clearly encompasses one or more genes which encode one or more proteins: e.g. "... DNA which includes a gene **or genes** coding for desired proteinaceous materials ..." (Abstract lines 1-4, with emphasis). Accordingly, although Axel lacks an antibody example, Axel nonetheless suggests recombinant antibody production in a suitable host (e.g. eukaryote).

4. The patentee presents the 132 Declaration of Dr. Douglas A. Rice to explain the relevance of the Rice and Baltimore, PNAS USA 79:7862 (1982) applied by the Examiner in the prior obviousness double patenting rejection. In this regard Dr. Rice explains that the reference's purpose was to gain a better understanding of mechanisms by which differentiated B cells regulate immunoglobulin expression; and that the reference does not explain how one might produce exogenous heavy and light chain in the 81A-2 strain which already endogenously produced heavy chain. Further, the Declarant argues that the reference's Ig tetramer was not properly assembled to produce a functional antibody.

These arguments were not deemed persuasive for the following reasons.

Initially it is again noted that in response to patentee's arguments against the reference(s) individually, one cannot show nonobviousness by attacking reference(s) individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Additionally, patentee's arguments are not commensurate to those instant Cabilly 2 claims that are not specifically limited to the feature upon which patentee relies (properly assembled "functional" antibody). Although the claims are interpreted in light

of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Further, the Rice reference clearly teaches to one of ordinary skill in the art that an exogenous immunoglobulin light chain assembles with a heavy chain endogenously produced by the cell even though both chains possess *different* antigen specificity. Thus, in light of this teaching it would be reasonable for one of ordinary skill in the art to expect that expressing a light and heavy chain of the *same* antigen specificity (e.g. derived from a known antibody) in a competent host would result in assembly of a functional antibody. See Declaration of David Baltimore submitted by the 3rd party with the 2nd Request for Reexamination.

Conclusion

Claims 1-36 of U.S. Pat. No. 6,331,415 are rejected.

Response Time and Extensions of Time

A shortened statutory period for response to this action is set to expire 2 month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an ex parte reexamination certificate in accordance with this action. 37 CFR 1.550(d).

Extensions of time in *ex parte* reexamination proceedings are provided for in 37 CFR 1.550(c). Extensions of time under 37 CFR 1.136 (a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to an applicant and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that *ex parte* reexamination proceedings "will be concluded with special dispatch" (37 CFR 1.555(a)).

Service on the Other Party (3rd Party Request)

After the filing of a request for reexamination by a 3rd party requester, any document filed by either the patent owner or the third party requester must be served on the other party (or parties where two or more third party requester proceedings are merged) in the reexamination proceeding in the manner provided in 37 CFR 1.248. See 37 CFR 1.550 (f).

Patent Owner Amendment

Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c).

Ongoing Duty To Disclose

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 6,331,415 throughout the course of this reexamination proceeding. The third party requester(s) is (are) also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Future Correspondences

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah D. Jones can be reached on 571-272-1535.

All correspondences relating to this ex parte reexamination proceeding should be directed as follows:

By **U.S. Postal Service Mail** to:

Mail Stop *Ex Parte* Reexam
ATTN: Central Reexamination Unit
Commissioner for Patents
P. O. Box 1450
Alexandria VA 22313-1450

By FAX to: (571) 273-9900
Central Reexamination Unit

By Hand to: Customer Service Window
Randolph Building, Lobby Level
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Alexandria, VA 22314

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Bennett Celsa
Primary Examiner
Art Unit 3991

Conferee:

Conferee: